09702165

ANSWER 2 OF 2 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1964:33231 CAPLUS
DOCUMENT NUMBER: 60:33231
ORIGINAL REFERENCE NO.: 60:5956e-f
TITLE: Cardiovascular lesions in Swiss mice fed a high-fat low-protein diet with and without betaine supplementation
AUTHOR(S): Ball, Carroll R.; Williams, W. Lane; Collum, Julius M.
CORPORATE SOURCE: Univ. of Mississippi School of Med., Jackson
SOURCE: Anat. Record (1963), 145, 49-59
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Young adult Taconic Swiss mice weighing at least 22 g. were placed on a diet contg. 8% casein, 28% lard, 57.5% sugar, 4% salt mixt. In addn., 2% betaine-HCl was added as a lipotropic supplement in the diet and fed to half the mice. After 7 weeks on the diet with or without the betaine supplement, myocardial necrosis and **thrombi** within atrial lumina occurred. By 13 weeks, the **thrombi** reached lethal size for 75% of the animals. Loss of wt. paralleled the development and progress of the cardiac lesions. Liver showed parenchymal liposis, which was less severe in mice receiving betaine. The betaine did not prevent or alter the cardiovascular lesions.

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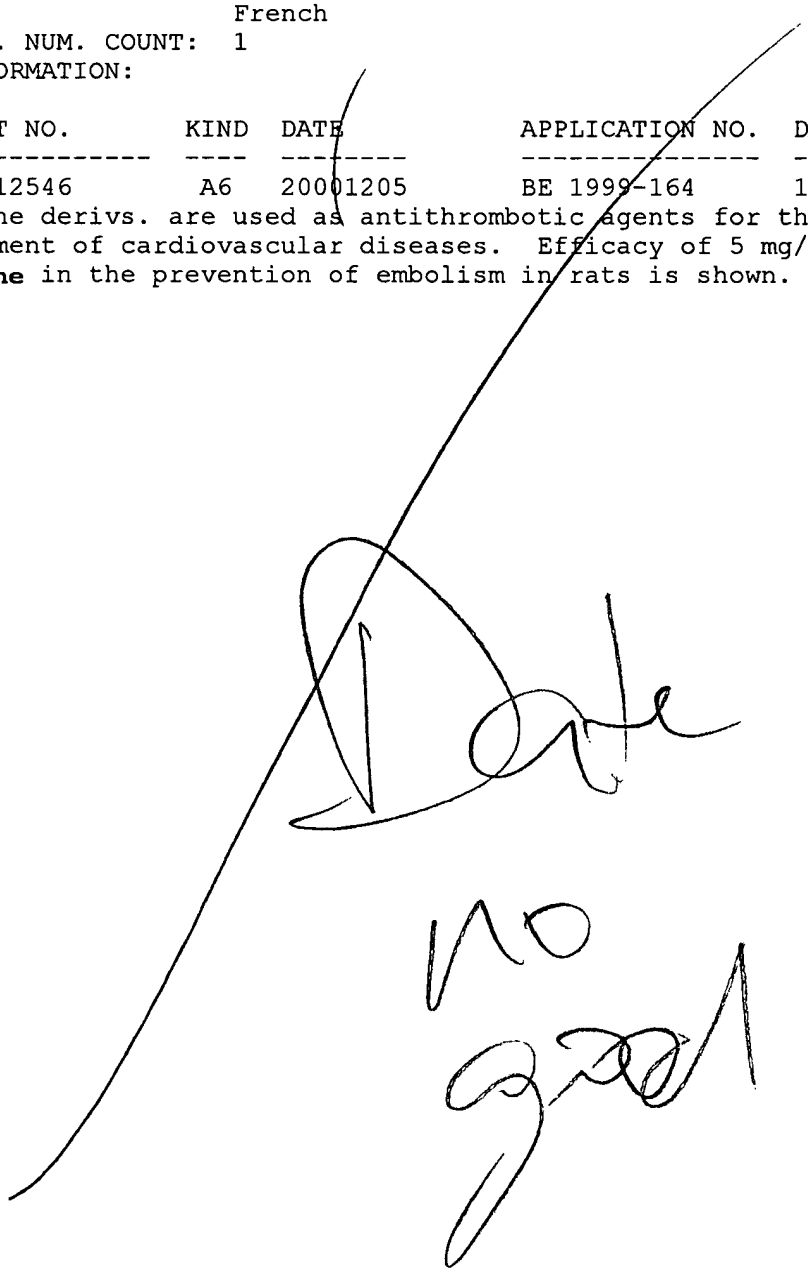
L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:343721 CAPLUS
DOCUMENT NUMBER: 136:319396
TITLE: Use of betaine derivatives as antithrombotic agents
PATENT ASSIGNEE(S): Messadek, Jallal, Belg.
SOURCE: Belg., 17 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 1012546	A6	20001205	BE 1999-164	19990310

AB Betaine derivs. are used as antithrombotic agents for the prevention or treatment of cardiovascular diseases. Efficacy of 5 mg/kg **glycine betaine** in the prevention of embolism in rats is shown.



09702165

L11 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:615384 CAPLUS
DOCUMENT NUMBER: 137:174926
TITLE: Pharmaceuticals containing **glycine betaine**
INVENTOR(S): Messadek, Jallal
PATENT ASSIGNEE(S): Belg.
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062322	A2	20020815	WO 2002-BE13	20020204
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002065320	A1	20020530	US 2001-945391	20010831

PRIORITY APPLN. INFO.:

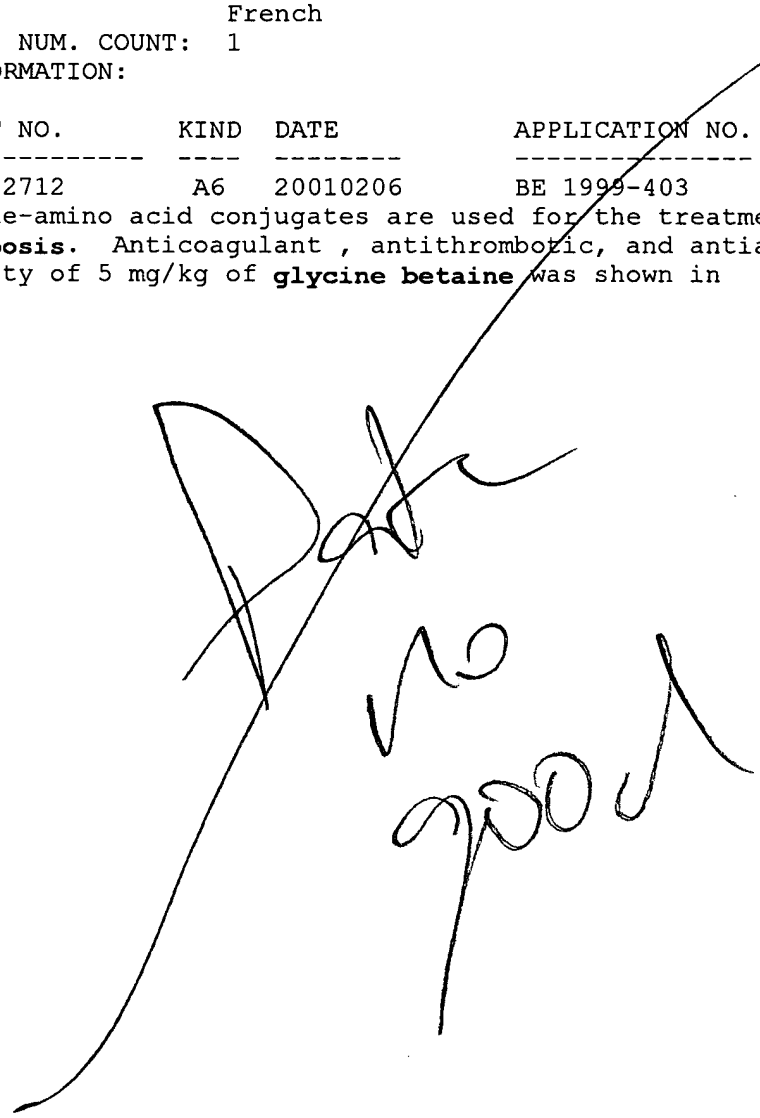
BE 2001-85	A	20010205
US 2001-945391	A	20010831
WO 2001-BE222	W	20011221
BE 1999-144	A	19990302
WO 2000-BE21	A2	20000301

09702165

L11 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:836201 CAPLUS
DOCUMENT NUMBER: 135:352796
TITLE: Use of betaine-amino acid conjugates for the treatment of ischemia and **thrombosis**
PATENT ASSIGNEE(S): Messadek, Jallal, Belg.
SOURCE: Belg., 18 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 1012712	A6	20010206	BE 1999-403	19990610

AB Betaine-amino acid conjugates are used for the treatment of ischemia and **thrombosis**. Anticoagulant , antithrombotic, and antiaggregation activity of 5 mg/kg of **glycine betaine** was shown in rats.



L11 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:627983 CAPLUS
DOCUMENT NUMBER: 133:187957
TITLE: Antithrombotic use of **glycine betaine**
INVENTOR(S): Messadek, Jallal
PATENT ASSIGNEE(S): Belg.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051596	A1	20000908	WO 2000-BE21	20000301
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BE 1012495	A3	20001107	BE 1999-144	19990302
EP 1156796	A1	20011128	EP 2000-907365	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008631	A	20020213	BR 2000-8631	20000301
US 2002065320	A1	20020530	US 2001-945391	20010831

PRIORITY APPLN. INFO.: BE 1999-144 A 19990302
WO 2000-BE21 W 20000301

AB The invention concerns the use of **glycine betaine** to eliminate physiopathol. vascular diseases. The invention concerns the curative and preventive activity of **glycine betaine** in the pathogenesis of **thromboembolic** and hemostatic diseases of arterial or venous origin. **Glycine betaine** has a preventing activity by inhibiting the formation of **thrombi** and a curative activity inhibiting the proliferation of **thrombi** by eliminating them. The invention is characterized in that **glycine betaine** does not present any risk of hemorrhage or allergy contrarily to mols. and treatments currently used. The invention also concerns the use of **glycine betaine** as anticoagulant for blood preservation.

09702165

L4 ANSWER 1 OF 31 MEDLINE
ACCESSION NUMBER: 2002408641 MEDLINE
DOCUMENT NUMBER: 22152024 PubMed ID: 12162390
TITLE: Sagittal sinus **thrombosis** in a teenager: homocystinuria associated with reversible antithrombin deficiency.
AUTHOR: Vorstman Ewoud; Keeling David; Leonard James; Pike Michael
SOURCE: DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY, (2002 Jul) 44 (7) 498.
Journal code: 0006761. ISSN: 0012-1622.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020807
Last Updated on STN: 20020824
Entered Medline: 20020823

L4 ANSWER 2 OF 31 MEDLINE
ACCESSION NUMBER: 2002161974 MEDLINE
DOCUMENT NUMBER: 21890856 PubMed ID: 11893229
TITLE: Drugs affecting homocysteine metabolism: impact on cardiovascular risk.
AUTHOR: Desouza Cyrus; Keebler Mary; McNamara Dennis B; Fonseca Vivian
CORPORATE SOURCE: Tulane University School of Medicine, New Orleans, USA.
SOURCE: DRUGS, (2002) 62 (4) 605-16. Ref: 77
Journal code: 7600076. ISSN: 0012-6667.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200204
ENTRY DATE: Entered STN: 20020315
Last Updated on STN: 20020424
Entered Medline: 20020423

AB Elevated total plasma homocysteine has been established as an independent risk factor for **thrombosis** and cardiovascular disease. A strong relationship between plasma homocysteine levels and mortality has been reported in patients with angiographically confirmed coronary artery disease. Homocysteine is a thiol containing amino acid. It can be metabolised by different pathways, requiring various enzymes such as cystathionine beta-synthase and methylenetetrahydrofolate reductase. These reactions also require several co-factors such as vitamin B6 and folate. Medications may interfere with these pathways leading to an alteration of plasma homocysteine levels. Several drugs have been shown to effect homocysteine levels. Some drugs frequently used in patients at risk of cardiovascular disease, such as the fibric acid derivatives used in certain dyslipidaemias and metformin in type 2 (non-insulin-dependent) diabetes mellitus, also raise plasma homocysteine levels. This elevation poses a theoretical risk of negating some of the benefits of these drugs. The mechanisms by which drugs alter plasma homocysteine levels vary. Drugs such as cholestyramine and metformin interfere with vitamin absorption from the gut. Interference with folate and homocysteine metabolism by methotrexate, nicotinic acid (niacin) and fibric acid derivatives, may lead to increased plasma homocysteine levels. Treatment with folate or vitamins B6 and B12 lowers plasma homocysteine levels effectively and is

relatively inexpensive. Although it still remains to be demonstrated that lowering plasma homocysteine levels reduces cardiovascular morbidity, surrogate markers for cardiovascular disease have been shown to improve with treatment of hyperhomocystenaemia. Would drugs like metformin, fibric acid derivatives and nicotinic acid be more effective in lowering cardiovascular morbidity and mortality, if the accompanying hyperhomocysteinaemia is treated? The purpose of this review is to highlight the importance of homocysteine as a risk factor, and examine the role and implications of drug induced modulation of homocysteine metabolism.

L4 ANSWER 3 OF 31 MEDLINE
ACCESSION NUMBER: 2002127043 MEDLINE
DOCUMENT NUMBER: 21845157 PubMed ID: 11857551
TITLE: Progressive cerebral edema associated with high methionine levels and betaine therapy in a patient with cystathionine beta-synthase (CBS) deficiency.
AUTHOR: Yaghmai Reza; Kashani Amir H; Geraghty Michael T; Okoh Jay; Pomper Martin; Tangerman Albert; Wagner Conrad; Stabler Sally P; Allen Robert H; Mudd S Harvey; Braverman Nancy
CORPORATE SOURCE: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
SOURCE: AMERICAN JOURNAL OF MEDICAL GENETICS, (2002 Feb 15) 108 (1) 57-63.
Journal code: 7708900. ISSN: 0148-7299.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020227
Last Updated on STN: 20020803
Entered Medline: 20020802

AB Cystathionine beta-synthase (CBS) deficiency, the most common form of homocystinuria, is an autosomal recessive inborn error of homocysteine metabolism. Treatment of B6-nonresponsive patients centers on lowering homocysteine and its disulfide derivatives (tHcy) by adherence to a methionine-restricted diet. However, lifelong dietary control is difficult. Betaine supplementation is used extensively in CBS-deficient patients to lower plasma tHcy. With betaine therapy, methionine levels increase over baseline, but usually remain below 1,500 micromol/L, and these levels have not been associated with adverse affects. We report a child with B6-nonresponsive CBS deficiency and dietary noncompliance whose methionine levels reached 3,000 micromol/L on betaine, and who subsequently developed massive cerebral edema without evidence of **thrombosis**. We investigated the etiology by determining methionine and betaine metabolites in our patient, and several possible mechanisms for her unusual response to betaine are discussed. We conclude that the cerebral edema was most likely precipitated by the betaine therapy, although the exact mechanism is uncertain. This case cautions physicians to monitor methionine levels in CBS-deficient patients on betaine and to consider betaine as an adjunct, not an alternative, to dietary control.

L4 ANSWER 4 OF 31 MEDLINE
ACCESSION NUMBER: 2001694749 MEDLINE
DOCUMENT NUMBER: 21607584 PubMed ID: 11742888
TITLE: Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically:

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a multicenter observational study.

AUTHOR: Yap S; Boers G H; Wilcken B; Wilcken D E; Brenton D P; Lee P J; Walter J H; Howard P M; Naughten E R

CORPORATE SOURCE: National Center for Inherited Metabolic Disorders, The Children's Hospital, Dublin, Ireland.

SOURCE: ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (2001 Dec) 21 (12) 2080-5.
Journal code: 9505803. ISSN: 1524-4636.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200201

ENTRY DATE: Entered STN: 20011217
Last Updated on STN: 20020125
Entered Medline: 20020103

AB An inborn error of metabolism, homocystinuria due to cystathionine beta-synthase deficiency, results in markedly elevated levels of circulating homocysteine. Premature vascular events are the main life-threatening complication. Half of all untreated patients have a vascular event by 30 years of age. We performed a multicenter observational study to assess the effectiveness of long-term homocysteine-lowering treatment in reducing vascular risk in 158 patients. Vascular outcomes were analyzed and effectiveness of treatment in reducing vascular risk was evaluated by comparison of actual to predicted number of vascular events, with the use of historical controls from a landmark study of 629 untreated patients with cystathionine beta-synthase deficiency. The 158 patients had a mean (range) age of 29.4 (4.5 to 70) years; 57 (36%) were more than 30 years old, and 10 (6%) were older than 50 years. There were 2822 patient-years of treatment, with an average of 17.9 years per patient. Plasma homocysteine levels were markedly reduced from pretreatment levels but usually remained moderately elevated. There were 17 vascular events in 12 patients at a mean (range) age of 42.5 (18 to 67) years: pulmonary embolism (n=3), myocardial infarction (n=2), deep venous **thrombosis** (n=5), cerebrovascular accident (n=3), transient ischemic attack (n=1), sagittal sinus **thrombosis** (n=1), and abdominal aortic aneurysm (n=2). Without treatment, 112 vascular events would have been expected, for a relative risk of 0.09 (95% CI 0.036 to 0.228; P<0.0001). Treatment regimens designed to lower plasma homocysteine significantly reduce cardiovascular risk in cystathionine beta-synthase deficiency despite imperfect biochemical control. These findings may be relevant to the significance of mild hyperhomocysteinemia that is commonly found in patients with vascular disease.

L4 ANSWER 5 OF 31 MEDLINE

ACCESSION NUMBER: 2001541435 MEDLINE

DOCUMENT NUMBER: 21472558 PubMed ID: 11588713

TITLE: [Orphan drugs and metabolic disorders].
Medicamentos huerfanos y enfermedades metabolicas.

AUTHOR: Martinez-Pardo M

CORPORATE SOURCE: Servicio de Pediatria; Hospital Ramon y Cajal, Madrid, 28006, Espana.. cmhd@eresmas.net

SOURCE: REVISTA DE NEUROLOGIA, (2001 Aug 1-15) 33 (3) 220-5. Ref: 13
Journal code: 7706841. ISSN: 0210-0010.

PUB. COUNTRY: Spain

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

09702165

(REVIEW, TUTORIAL)
LANGUAGE: Spanish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20011008
Last Updated on STN: 20020717
Entered Medline: 20020716

AB INTRODUCTION: Over the past twenty years the legal and philosophical concept of orphan diseases has developed to include the diseases with an incidence in the general population of less than 1/5,000. Treatment of these conditions, which is very specific, requires drugs which will be used by a very small number of patients and are therefore not profitable from the financial point of view. This gives rise to the concept of orphan drugs which lack sponsorship, are expensive to investigate and develop, are little used and therefore there is little incentive to market them. All metabolic disorders due to genetic defects may be considered to be orphan diseases , since their incidence in the population is less than 1/5,000 and there may be only a negligible incidence of 1/37,000,000. DEVELOPMENT: In this study we discuss the treatment of three orphan metabolic diseases, which severely affect the central nervous system by different mechanisms, by three orphan drugs which solve the problems of only a few patients. We describe the treatment of: (1) the deficiency of the synthesis of tetrahydrobiopterin, which causes neurotransmitter deficiency, with tetrahydrobiopterin, (2) N acetylglutamate sythetase deficiency, which causes severe hyperammonaemia and cerebral oedema, with N carbamyl glutamate (3) cystathionine synthetase deficiency which causes hyperhomocyteinaemia and a high risk of **thromboembolic** accidents, with Betaine.

L4 ANSWER 6 OF 31 MEDLINE
ACCESSION NUMBER: 2001043694 MEDLINE
DOCUMENT NUMBER: 20480269 PubMed ID: 11027169
TITLE: Osmoprotective effect of glycine betaine on **thrombopoietin** production in hyperosmotic Chinese hamster ovary cell culture: clonal variations.
AUTHOR: Kim T K; Ryu J S; Chung J Y; Kim M S; Lee G M
CORPORATE SOURCE: Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Kusong-Dong 373-1, Yusong-Gu, Taejon 305-701, Korea.
SOURCE: BIOTECHNOLOGY PROGRESS, (2000 Sep-Oct) 16 (5) 775-81. Journal code: 8506292. ISSN: 8756-7938.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001204

AB When 23 recombinant Chinese hamster ovary (rCHO) cell clones were cultivated in hyperosmolar medium resulting from NaCl addition (533 mOsm/kg), their specific **thrombopoietin** (TPO) productivity (q(TPO)) was increased. However, due to depressed cell growth at elevated osmolality, no enhancement in the maximum TPO titer was made in batch cultures of all 23 clones. To test the feasibility of using glycine betaine, known as a strong osmoprotective compound, for improved TPO production in hyperosmotic rCHO cell cultures, hyperosmotic batch cultures of 23 clones were performed in the presence of 15 mM glycine betaine. Glycine betaine was found to have a strong osmoprotective effect on all 23 clones. Inclusion of 15 mM glycine betaine in hyperosmolar medium enabled

22 clones to grow at 542 mOsm/kg, where most clones could not grow in the absence of glycine betaine, but at a cost of reduced q(TPO). However, the relative decrease in q(TPO) varied significantly among clones. Thus, efficacy of the simultaneous use of hyperosmotic pressure and glycine betaine as a means to improve foreign protein production was variable among clones. Six out of 23 clones displayed more than a 40% increase in the maximum TPO titer in the hyperosmolar medium containing glycine betaine, compared with that in the standard medium with a physiological osmolality. Taken together, the results obtained here emphasize the importance of selection of clones for the successful use of hyperosmotic pressure and glycine betaine as an economical means to improve TPO production.

L4 ANSWER 7 OF 31 MEDLINE
ACCESSION NUMBER: 2001039986 MEDLINE
DOCUMENT NUMBER: 20427764 PubMed ID: 10972928
TITLE: Osmoprotective effect of glycine betaine on foreign protein production in hyperosmotic recombinant chinese hamster ovary cell cultures differs among cell lines.
AUTHOR: Ryu J S; Kim T K; Chung J Y; Lee G M
CORPORATE SOURCE: Department of Biological Sciences, Korea Advanced Institute of Science and Technology 373-1, Kusong-Dong, Yusong-Gu, Taejon 305-701, Korea.
SOURCE: BIOTECHNOLOGY AND BIOENGINEERING, (2000 Oct 20) 70 (2) 167-75.
Journal code: 7502021. ISSN: 0006-3592.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001207

AB When three recombinant Chinese hamster ovary (rCHO) cell lines, CHO/dhfr-B22-4, CS13-1.00*, and CS13-0.02*, were cultivated in hyperosmolar media resulting from NaCl addition, their specific foreign protein productivity increased with medium osmolality. However, due to a simultaneous suppression of cell growth at elevated osmolality, no enhancement in the maximum foreign protein titer was made in batch cultures. To test the feasibility of using glycine betaine, known as a strong osmoprotective compound, for improved foreign protein production in hyperosmotic rCHO cell cultures, hyperosmotic batch cultures were carried out in the presence of 15 mM glycine betaine. Glycine betaine was found to have a strong osmoprotective effect on all three rCHO cell lines. Inclusion of 15 mM glycine betaine in hyperosmolar medium enabled rCHO cell lines to grow at 557 to 573 mOsm/kg, whereas they could not grow in the absence of glycine betaine. However, effect of glycine betaine inclusion in hyperosmolar medium on foreign protein production differed among rCHO cell lines. CHO/dhfr-B22-4 cells retained enhanced specific human **thrombopoietin** (hTPO) productivity in the presence of glycine betaine, and thereby the maximum hTPO titer obtained at 573 mOsm/kg was increased by 72% over that obtained in the control culture with physiological osmolality (292 mOsm/kg). On the other hand, enhanced specific antibody productivity of CS13-1.00* and CS13-0.02* at elevated osmolality was decreased significantly in the presence of glycine betaine. As a result, the maximum antibody titer at 557 mOsm/kg was similar to that obtained in the control culture with physiological osmolality. The mRNA contents per cell determined by northern blot hybridization correlated with q in all three rCHO cell lines, indicating that transcriptional

regulation is responsible in part for q enhancement at hyperosmolality in the absence as well as the presence of glycine betaine. Taken together, efficacy of the simultaneous use of hyperosmotic pressure and glycine betaine as a means to improve foreign protein production was variable among different rCHO cell lines.

L4 ANSWER 8 OF 31 MEDLINE
ACCESSION NUMBER: 2000415759 MEDLINE
DOCUMENT NUMBER: 20291371 PubMed ID: 10828477
TITLE: Tissue factor pathway inhibitor levels in patients with homocystinuria.
AUTHOR: Cella G; Burlina A; Sbarai A; Motta G; Girolami A; Berrettini M; Strauss W
CORPORATE SOURCE: II Department of Medicine, University of Padua Medical School, Italy.
SOURCE: THROMBOSIS RESEARCH, (2000 Jun 1) 98 (5) 375-81.
Journal code: 0326377. ISSN: 0049-3848.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000830

AB **Thrombotic** events are a well-recognized complication of homocystinuria. However, the mechanisms involved in the atherogenic and **thrombotic** effects of homocyst(e)ine remain incompletely understood. The objective of this study was to determine the role of endothelial cell activation/damage as indicated by levels of **thrombomodulin**, tissue factor and tissue factor pathway inhibitor, and factor VII activity in patients with homocystinuria. Six patients with homocystinuria, nonresponsive to pyridoxine, treated only with trimethylglycine (betaine) were injected with a bolus of 20 IU/kg body weight of unfractionated commercial heparin to induce the release of tissue factor pathway inhibitor from the vascular endothelium. Tissue factor, **thrombomodulin**, and factor VII activity were measured by enzyme-linked immunosorbent assay and clotting assay before heparin administration. Tissue factor pathway inhibitor antigen and activity were measured before and 5 minutes after the bolus of heparin. Levels of homocyst(e)ine were elevated (patients: 144.2+/-19.2 micromol/L; controls: 10.2+/-0.9 micromol/L); however, levels of **thrombomodulin**, tissue factor, and tissue factor pathway inhibitor antigen were not statistically different from the control group. In contrast, tissue factor pathway inhibitor activity showed a significantly increased level (patients: 2.09+/-0.34 U/L; controls: 1.14+/-0.20 U/L; $p<0.05$) that was correlated with homocyst(e)ine. Factor VII activity was significantly decreased (patients: 64.7+/-5.1%; controls: 91.4+/-4.7%; $p<0.05$) and inversely correlated with homocyst(e)ine. After heparin the patients released higher amounts of tissue factor pathway inhibitor antigen and activity compared with the control group; however, the difference was not statistically significant. Although not treated with antithrombotic drugs, none of the patients had any **thromboembolic** complications after starting betaine. In addition to betaine treatment, the enhanced factor pathway inhibitor antigen activity observed in this small series of patients suggests that factor pathway inhibitor antigen may play an additional, as yet unexplained, role in this genetic disorder.

L4 ANSWER 9 OF 31 MEDLINE

09702165

ACCESSION NUMBER: 1999294582 MEDLINE
DOCUMENT NUMBER: 99294582 PubMed ID: 10364517
TITLE: The molecular basis of cystathionine beta-synthase deficiency in Dutch patients with homocystinuria: effect of CBS genotype on biochemical and clinical phenotype and on response to treatment.
AUTHOR: Kluijtmans L A; Boers G H; Kraus J P; van den Heuvel L P; Cruysberg J R; Trijbels F J; Blom H J
CORPORATE SOURCE: Departments of Pediatrics, University Hospital Nijmegen, The Netherlands.
SOURCE: AMERICAN JOURNAL OF HUMAN GENETICS, (1999 Jul) 65 (1) 59-67.
Journal code: 0370475. ISSN: 0002-9297.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990805

data no good

AB Homocystinuria due to cystathionine beta-synthase (CBS) deficiency, inherited as an autosomal recessive trait, is the most prevalent inborn error of methionine metabolism. Its diverse clinical expression may include ectopia lentis, skeletal abnormalities, mental retardation, and premature arteriosclerosis and **thrombosis**. This variability is likely caused by considerable genetic heterogeneity. We investigated the molecular basis of CBS deficiency in 29 Dutch patients from 21 unrelated pedigrees and studied the possibility of a genotype-phenotype relationship with regard to biochemical and clinical expression and response to homocysteine-lowering treatment. Clinical symptoms and biochemical parameters were recorded at diagnosis and during long-term follow-up. Of 10 different mutations detected in the CBS gene, 833T-->C (I278T) was predominant, present in 23 (55%) of 42 independent alleles. At diagnosis, homozygotes for this mutation (n=12) tended to have higher homocysteine levels than those seen in patients with other genotypes (n=17), but similar clinical manifestations. During follow-up, I278T homozygotes responded more efficiently to homocysteine-lowering treatment. After 378 patient-years of treatment, only 2 vascular events were recorded; without treatment, at least 30 would have been expected (P<.01). This intervention in Dutch patients significantly reduces the risk of cardiovascular disease and other sequelae of classical homocystinuria syndrome.

L4 ANSWER 10 OF 31 MEDLINE
ACCESSION NUMBER: 1998142723 MEDLINE
DOCUMENT NUMBER: 98142723 PubMed ID: 9481724
TITLE: No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinaemia in haemodialysis patients.
AUTHOR: van Guldener C; Janssen M J; Lambert J; ter Wee P M; Jakobs C; Donker A J; Stehouwer C D
CORPORATE SOURCE: Department of Internal Medicine, University Hospital, Vrije Universiteit, Amsterdam, The Netherlands.
SOURCE: NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1998 Jan) 13 (1) 106-12.
Journal code: 8706402. ISSN: 0931-0509.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)

09702165

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980326
Last Updated on STN: 19980326
Entered Medline: 19980319

AB BACKGROUND: Hyperhomocysteinaemia is frequent in chronic haemodialysis patients. Because of its potential role in athero- and **thrombogenesis**, the effects of long-term homocysteine-lowering treatment on endothelial function are of interest. METHODS: We conducted a randomized, controlled trial in 35 haemodialysis patients. In phase 1, patients were treated with 5 mg folic acid or 5 mg folic acid and 4 g betaine per day for 12 weeks, and in phase 2 with 1 or 5 mg folic acid daily for 40 weeks. In phase 3, all patients received 15 mg folic acid daily for four weeks. Endothelial function was assessed before and after 52 weeks of treatment by determination of flow-mediated vasodilatation of the brachial artery, and by measuring plasma levels of endothelium-derived proteins. RESULTS: Non-fasting predialysis plasma total homocysteine was markedly elevated at baseline (46.9 +/- 6.3 mumol/l) and decreased rapidly after initiation of therapy. Significant differences in plasma homocysteine between the groups were found neither during phase 1 nor phase 2. Plasma total homocysteine had normalized in only two out of 30 patients at the end of phase 2. Increasing the daily folic acid dose to 15 mg did not further reduce plasma total homocysteine. Endothelial function parameters did not improve. CONCLUSIONS: We concluded that betaine is not effective in conjunction with folic acid in the treatment of hyperhomocysteinaemia in haemodialysis patients. Normalization of plasma total homocysteine is seldom achieved with 1, 5 or 15 mg folic acid daily, which may explain why long-term homocysteine-lowering treatment with 1 or 5 mg folic acid does not ameliorate endothelial function.

L4 ANSWER 11 OF 31 MEDLINE
ACCESSION NUMBER: 1998058607 MEDLINE
DOCUMENT NUMBER: 98058607 PubMed ID: 9397998
TITLE: Cytoprotection by the osmolytes betaine and taurine in ischemia-reoxygenation injury in the perfused rat liver.
AUTHOR: Wettstein M; Haussinger D
CORPORATE SOURCE: Clinic for Gastroenterology, Hepatology, and Infectiology, Heinrich-Heine-University, Dusseldorf, Germany.
SOURCE: HEPATOLOGY, (1997 Dec) 26 (6) 1560-6.
Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980122
Last Updated on STN: 19980122
Entered Medline: 19980108

AB Medium osmolarity sensitively regulates Kupffer cell functions like phagocytosis and prostaglandin (PG) and cytokine production. Betaine and taurine, recently identified as osmolytes in liver cells, interfere with these effects. Because Kupffer cell activation is an important pathogenic mechanism in ischemia-reoxygenation injury, the influence of osmolarity and osmolytes was investigated in a rat liver perfusion model of warm ischemia. Livers were perfused with different medium osmolarities for 60 to 90 minutes in the absence of oxygen, followed by another 90 minutes of reoxygenation. Lactate dehydrogenase (LDH) leakage into the effluent perfusate during the hypoxic and the reoxygenation period was eight- to 10-fold higher with a medium osmolarity of 385 mosmol/L than in

normo-osmolarity, and further decreased with hypo-osmolar perfusion buffer. Betaine and taurine addition to the perfusate in near physiological concentrations decreased hypoxia-reoxygenation-induced LDH leakage, aspartate transaminase (AST) leakage, and perfusion pressure increase in hyperosmolar and normo-osmolar perfusions. Stimulation of PGD2, PGE2, **thromboxane** B2 (TXB2), and tumor necrosis factor alpha (TNF-alpha) release, as well as induction of carbon uptake by the liver during reoxygenation, were suppressed by betaine and taurine, pointing to an interference of these osmolytes with Kupffer cell function. In contrast, endothelial cell function as assessed by hyaluronic acid (HA) uptake was not influenced. It is concluded that warm ischemia-reoxygenation injury in rat liver is aggravated by hyperosmolarity and attenuated by hypo-osmolarity. The osmolytes betaine and taurine have a protective effect, presumably by inhibition of Kupffer cell activation.

L4 ANSWER 12 OF 31 MEDLINE
ACCESSION NUMBER: 97467264 MEDLINE
DOCUMENT NUMBER: 97467264 PubMed ID: 9323245
TITLE: Homocystinuria presenting with portal vein **thrombosis** and pancreatic pseudocyst: a case report.
AUTHOR: Hong H S; Lee H K; Kwon K H
CORPORATE SOURCE: Department of Radiology, College of Medicine, Soonchunhyang University Hospital, Hannam Dong 657 Yongsan Gu, Seoul 140-743, Korea.
SOURCE: PEDIATRIC RADIOLOGY, (1997 Oct) 27 (10) 802-4. Journal code: 0365332. ISSN: 0301-0449.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971202
AB Homocystinuria is a rare, inherited metabolic disease frequently associated with severe multisystemic involvement such as dislocated lenses, skeletal deformities, mental retardation, and premature vascular occlusion. Arterial and venous **thromboembolic** events present frequent and life-threatening complications in homocystinuric patients. It has been suggested that mild homocystinemia would be a risk factor for vascular disease.

L4 ANSWER 13 OF 31 MEDLINE
ACCESSION NUMBER: 92306342 MEDLINE
DOCUMENT NUMBER: 92306342 PubMed ID: 1819467
TITLE: Betaine:homocysteine methyltransferase--a new assay for the liver enzyme and its absence from human skin fibroblasts and peripheral blood lymphocytes.
AUTHOR: Wang J A; Dudman N P; Lynch J; Wilcken D E
CORPORATE SOURCE: Department of Cardiovascular Medicine, Prince Henry Hospital, University of New South Wales, Sydney, Australia.
SOURCE: CLINICA CHIMICA ACTA, (1991 Dec 31) 204 (1-3) 239-49. Journal code: 1302422. ISSN: 0009-8981.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199207
ENTRY DATE: Entered STN: 19920807

Last Updated on STN: 19920807
Entered Medline: 19920730

AB Chronic elevation of plasma homocysteine is associated with increased atherogenesis and **thrombosis**, and can be lowered by betaine (N,N,N-trimethylglycine) treatment which is thought to stimulate activity of the enzyme betaine:homocysteine methyltransferase. We have developed a new assay for this enzyme, in which the products of the enzyme-catalysed reaction between betaine and homocysteine are oxidised by performic acid before being separated and quantified by amino acid analysis. This assay confirmed that human liver contains abundant betaine:homocysteine methyltransferase (33.4 nmol/h/mg protein at 37 degrees C, pH 7.4). Chicken and lamb livers also contain the enzyme, with respective activities of 50.4 and 6.2 nmol/h/mg protein. However, phytohaemagglutinin-stimulated human peripheral blood lymphocytes and cultured human skin fibroblasts contained no detectable betaine:homocysteine methyltransferase (less than 1.4 nmol/h/mg protein), even after cells were pre-cultured in media designed to stimulate production of the enzyme. The results emphasize the importance of the liver in mediating the lowering of elevated circulating homocysteine by betaine.

L4 ANSWER 14 OF 31 MEDLINE
ACCESSION NUMBER: 66039238 MEDLINE
DOCUMENT NUMBER: 66039238 PubMed ID: 5842161
TITLE: Spontaneous and dietary-induced cardiovascular lesions in DBA mice.
AUTHOR: Ball C R; Williams W L
SOURCE: ANATOMICAL RECORD, (1965 Jun) 152 (2) 199-209.
Journal code: 0370540. ISSN: 0003-276X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196601
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19970203
Entered Medline: 19660125

L4 ANSWER 15 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:615384 CAPLUS
DOCUMENT NUMBER: 137:174926
TITLE: Pharmaceuticals containing glycine betaine
INVENTOR(S): Messadek, Jallal
PATENT ASSIGNEE(S): Belg.
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062322	A2	20020815	WO 2002-BE13	20020204

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,

TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
US 2002065320 A1 20020530 US 2001-945391 20010831
PRIORITY APPLN. INFO.: BE 2001-85 A 20010205
US 2001-945391 A 20010831
WO 2001-BE222 W 20011221
BE 1999-144 A 19990302
WO 2000-BE21 A2 20000301
OTHER SOURCE(S): MARPAT 137:174926
AB A pharmaceutical combination comprises a drug with at 1 hemorrhagic side effect, and an effective amt. of Me3N+(CH2)nCO2- (where n = 1-5) for preventing or reducing the hemorrhagic side effect. Tablets contained glycine betaine 200, hydrogenated vegetable oil 200, purified talc 12.63, Mg stearate 8.42 mg/tablet. The tablets were assessed by dissoln. properties by using a paddle method.

L4 ANSWER 16 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:343721 CAPLUS
DOCUMENT NUMBER: 136:319396
TITLE: Use of betaine derivatives as antithrombotic agents
PATENT ASSIGNEE(S): Messadek, Jallal, Belg.
SOURCE: Belg., 17 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 1012546	A6	20001205	BE 1999-164	19990310

AB Betaine derivs. are used as antithrombotic agents for the prevention or treatment of cardiovascular diseases. Efficacy of 5 mg/kg glycine betaine in the prevention of embolism in rats is shown.

L4 ANSWER 17 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:3254 CAPLUS
DOCUMENT NUMBER: 136:226604
TITLE: Vascular outcome in patients with homocystinuria due to cystathionine .beta.-synthase deficiency treated chronically: a multicenter observational study
AUTHOR(S): Yap, Sufin; Boers, Godfried H. J.; Wilcken, Bridget; Wilcken, David E. L.; Brenton, David P.; Lee, Philip J.; Walter, John H.; Howard, Pamela M.; Naughten, Eileen R.
CORPORATE SOURCE: Natl. Cent. Inherited Metab. Disorders, Children's Hosp., Dublin, Ire.
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2001), 21(12), 2080-2085
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An inborn error of metab., homocystinuria due to cystathionine .beta.-synthase deficiency, results in markedly elevated levels of circulating homocysteine. Premature vascular events are the main life-threatening complication. Half of all untreated patients have a vascular event by 30 yr of age. We performed a multicenter observational

study to assess the effectiveness of long-term homocysteine-lowering treatment in reducing vascular risk in 158 patients. Vascular outcomes were analyzed and effectiveness of treatment in reducing vascular risk was evaluated by comparison of actual to predicted no. of vascular events, with the use of historical controls from a landmark study of 629 untreated patients with cystathionine .beta.-synthase deficiency. The 158 patients had a mean (range) age of 29.4 (4.5 to 70) years: 57 (36%) were more than 30 yr old, and 10 (6%) were older than 50 yr. There were 2822 patient-years of treatment, with an av. of 17.9 yr per patient. Plasma homocysteine levels were markedly reduced from pretreatment levels but usually remained moderately elevated. There were 17 vascular events in 12 patients at a mean (range) age of 42.5 (18 to 67) years: pulmonary embolism (n=3). myocardial infarction (n=2). deep venous **thrombosis** (n =5). cerebrovascular accident (n=3), transient ischemic attack (n=1), sagittal sinus **thrombosis** (n= 1), and abdominal aortic aneurysm (n=2). Without treatment. 112 vascular events would have been expected, for a relative risk of 0.09 (95% Cl 0.036 to 0.228; P<0.0001). Treatment regimens designed to lower plasma homocysteine significantly reduce cardiovascular risk in cystathionine .beta.-synthase deficiency despite imperfect biochem. control. These findings may be relevant to the significance of mild hyperhomocysteinemia that is commonly found in patients with vascular disease.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:836201 CAPLUS
DOCUMENT NUMBER: 135:352796
TITLE: Use of betaine-amino acid conjugates for the treatment of ischemia and **thrombosis**
PATENT ASSIGNEE(S): Messadek, Jallal, Belg.
SOURCE: Belg., 18 pp.
CODEN: BEXXAL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
BE 1012712	A6	20010206	BE 1999-403	19990610

AB Betaine-amino acid conjugates are used for the treatment of ischemia and **thrombosis**. Anticoagulant , antithrombotic, and antiaggregation activity of 5 mg/kg of glycine betaine was shown in rats.

L4 ANSWER 19 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:81096 CAPLUS
DOCUMENT NUMBER: 134:247106
TITLE: Decrease of plasma taurine in Gaucher disease and its sustained correction during enzyme replacement therapy
AUTHOR(S): vom Dahl, S.; Monnighoff, I.; Haussinger, D.
CORPORATE SOURCE: Division of Gastroenterology, Hepatology and Infectious Diseases, Heinrich-Heine-University, Dusseldorf, Germany
SOURCE: Amino Acids (2000), 19(3-4), 585-592
CODEN: AACIE6; ISSN: 0939-4451
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Gaucher disease is caused by an autosomal-recessive deficiency of

glucocerebrosidase. Cells of monocytic/macrophagic origin accumulate glucosylceramide. This leads to hepatosplenomegaly, bone destruction, **thrombocytopenia** and anemia. Enzyme replacement therapy (ERT) with macrophage-targeted glucocerebrosidase leads to normalization of these parameters. The way of macrophage activation in Gaucher disease is not known. Recently, the osmolytes taurine, betaine and inositol were identified as important regulators of macrophage function in liver. Therefore, the role of plasma taurine in Gaucher disease as a primarily macrophage-derived disease was studied. Fasting plasma levels were measured from blood samples of healthy control subjects (n = 29, m:f = 11:18, mean age 37 .+-. 3 yr), from untreated Gaucher patients (n = 16, m:f = 7:9, mean age 44 .+-. 4 yr) and those treated for 37 .+-. 2 mo (n = 54, m:f = 19:35, mean age 47 .+-. 2 yr). Amino acid anal. was carried out in a BioChrom amino acid analyzer. In the untreated patients, plasma taurine was 45 .+-. 3.mu.M, as compared to the controls with a plasma taurine of 63 .+-. 4.mu.M ($p < 0.01$). The av. increase of plasma taurine during the first year of ERT was 18 .+-. 8.mu.M (n = 10). Patients treated for an av. of 37 mo (range 1-9 yr of ERT) had a plasma taurine of 65 .+-. 4.mu.M (n = 54), which was not different from the controls. It is concluded that Gaucher patients show decreased plasma taurine levels and that therapy of Gaucher disease might correct this. It has to be established, whether decreased taurine availability is a cofactor of the permanent activation of glucosylceramide-storing monocytes/macrophages in this disease.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:700440 CAPLUS
DOCUMENT NUMBER: 133:361969
TITLE: Osmoprotective effect of glycine betaine on foreign protein production in hyperosmotic recombinant chinese hamster ovary cell cultures differs among cell lines
AUTHOR(S): Ryu, Joon Soo; Kim, Tae Kyung; Chung, Joo Young; Lee, Gyun Min
CORPORATE SOURCE: Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Taejon, 305-701, S. Korea
SOURCE: Biotechnology and Bioengineering (2000), 70(2), 167-175
CODEN: BIBIAU; ISSN: 0006-3592
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When three recombinant Chinese hamster ovary (rCHO) cell lines, CHO/dhfr-B22-4, CS13-1.00*, and CS13-0.02*, were cultivated in hyperosmolar media resulting from NaCl addn., their specific foreign protein productivity increased with medium osmolality. However, due to a simultaneous suppression of cell growth at elevated osmolality, no enhancement in the max. foreign protein titer was made in batch cultures. To test the feasibility of using glycine betaine, known as a strong osmoprotective compd., for improved foreign protein prodn. in hyperosmotic rCHO cell cultures, hyperosmotic batch cultures were carried out in the presence of 15 mM glycine betaine. Glycine betaine was found to have a strong osmoprotective effect on all three rCHO cell lines. Inclusion of 15 mM glycine betaine in hyperosmolar medium enabled rCHO cell lines to grow at 557 to 573 mOsm/kg, whereas they could not grow in the absence of glycine betaine. However, effect of glycine betaine inclusion in hyperosmolar medium on foreign protein prodn. differed among rCHO cell lines. CHO/dhfr-B22-4 cells retained enhanced specific human

thrombopoietin (hTPO) productivity in the presence of glycine betaine, and thereby the max. hTPO titer obtained at 573 mOsm/kg was increased by 72% over that obtained in the control culture with physiol. osmolality (292 mOsm/kg). On the other hand, enhanced specific antibody productivity of CS13-1.00* and CS13-0.02* at elevated osmolality was decreased significantly in the presence of glycine betaine. As a result, the max. antibody titer at 557 mOsm/kg was similar to that obtained in the control culture with physiol. osmolality. The mRNA contents per cell detd. by northern blot hybridization correlated with q in all three rCHO cell lines, indicating that transcriptional regulation is responsible in part for q enhancement at hyperosmolality in the absence as well as the presence of glycine betaine. Taken together, efficacy of the simultaneous use of hyperosmotic pressure and glycine betaine as a means to improve foreign protein prodn. was variable among different rCHO cell lines.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 21 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:632650 CAPLUS
DOCUMENT NUMBER: 133:321053
TITLE: Osmoprotective Effect of Glycine Betaine on **Thrombopoietin** Production in Hyperosmotic Chinese Hamster Ovary Cell Culture: Clonal Variations
AUTHOR(S): Kim, Tae Kyung; Ryu, Joon Soo; Chung, Joo Young; Kim, Min Soo; Lee, Gyun Min
CORPORATE SOURCE: Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Taejon, 305-701, S. Korea
SOURCE: Biotechnology Progress (2000), 16(5), 775-781
CODEN: BIPRET; ISSN: 8756-7938
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB When 23 recombinant Chinese hamster ovary (rCHO) cell clones were cultivated in hyperosmolar medium resulting from NaCl addn. (533 mOsm/kg), their specific **thrombopoietin** (TPO) productivity (qTPO) was increased. However, due to depressed cell growth at elevated osmolality, no enhancement in the max. TPO titer was made in batch cultures of all 23 clones. To test the feasibility of using glycine betaine, known as a strong osmoprotective compd., for improved TPO prodn. in hyperosmotic rCHO cell cultures, hyperosmotic batch cultures of 23 clones were performed in the presence of 15 mM glycine betaine. Glycine betaine was found to have a strong osmoprotective effect on all 23 clones. Inclusion of 15 mM glycine betaine in hyperosmolar medium enabled 22 clones to grow at 542 mOsm/kg, where most clones could not grow in the absence of glycine betaine, but at a cost of reduced qTPO. However, the relative decrease in qTPO varied significantly among clones. Thus, efficacy of the simultaneous use of hyperosmotic pressure and glycine betaine as a means to improve foreign protein prodn. was variable among clones. Six out of 23 clones displayed more than a 40% increase in the max. TPO titer in the hyperosmolar medium contg. glycine betaine, compared with that in the std. medium with a physiol. osmolality. Taken together, the results obtained here emphasize the importance of selection of clones for the successful use of hyperosmotic pressure and glycine betaine as an economical means to improve TPO prodn.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:627983 CAPLUS

09702165

DOCUMENT NUMBER: 133:187957
TITLE: Antithrombotic use of glycine betaine
INVENTOR(S): Messadek, Jallal
PATENT ASSIGNEE(S): Belg.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051596	A1	20000908	WO 2000-BE21	20000301
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BE 1012495	A3	20001107	BE 1999-144	19990302
EP 1156796	A1	20011128	EP 2000-907365	20000301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2000008631	A	20020213	BR 2000-8631	20000301
US 2002065320	A1	20020530	US 2001-945391	20010831

PRIORITY APPLN. INFO.: BE 1999-144 A 19990302
WO 2000-BE21 W 20000301

AB The invention concerns the use of glycine betaine to eliminate physiopathol. vascular diseases. The invention concerns the curative and preventive activity of glycine betaine in the pathogenesis of **thromboembolic** and hemostatic diseases of arterial or venous origin. Glycine betaine has a preventing activity by inhibiting the formation of **thrombi** and a curative activity inhibiting the proliferation of **thrombi** by eliminating them. The invention is characterized in that glycine betaine does not present any risk of hemorrhage or allergy contrarily to mols. and treatments currently used. The invention also concerns the use of glycine betaine as anticoagulant for blood preservation.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:535000 CAPLUS
DOCUMENT NUMBER: 133:140269
TITLE: Pharmaceutical combination of progesterone and folic acid
INVENTOR(S): Bogye, Gabor
PATENT ASSIGNEE(S): Hung.
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000044385	A1	20000803	WO 2000-HU9	20000128

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1148882	A1	20011031	EP 2000-903916	20000128

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:	HU 1999-213	A	19990201
	WO 2000-HU9	W	20000128

AB The present invention relates to pharmaceutical compn.(s) comprising gestogen type steroid hormone(s) and compd.(s) lowering in human plasma the level of homocysteine, capable of lowering the risk of **thromboembolic** side effects of gestogen type compns. The plasma homocysteine content reducing agents may be selected from folic acid, vitamin B6, vitamin B12, betaine, choline, acetyl cysteine and metabolic precursors, analogs and/or derivs. thereof. Clin examples were given showing lowering of plasma homocysteine levels after administration of folic acid and vitamin B6 along with compds. which increase homocysteine levels such as levonorgestrel-ethinylestradiol combination. Folic acid (1 or 3 mg) or 20 mg vitamin B6 were added to tablet compns. contg., e.g., levonorgestrel 0.15 and ethinylestradiol 0.03 mg.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 31 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER:	2000:314527 CAPLUS
DOCUMENT NUMBER:	132:326078
TITLE:	Compositions for the treatment and prevention of cardiovascular diseases
INVENTOR(S):	Buchholz, Herwig; Meduski, Jerzy D.
PATENT ASSIGNEE(S):	Merck Patent G.m.b.H., Germany
SOURCE:	PCT Int. Appl., 18 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000025764	A2	20000511	WO 1999-EP7689	19991013
WO 2000025764	A3	20000713		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9964709	A1	20000522	AU 1999-64709	19991013
BR 9914815	A	20010703	BR 1999-14815	19991013

EP 1124548 A2 20010822 EP 1999-952559 19991013
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2002528488 T2 20020903 JP 2000-579205 19991013
PRIORITY APPLN. INFO.: US 1998-106205P P 19981030
WO 1999-EP7689 W 19991013

AB Compns. comprising one or more active ingredients and, optionally, one or more nutritional substances, solid, liq. and/or semiliquid excipients or auxiliaries, wherein the active ingredients consist of a) a consisting of one or more compds. selected from Me and methylene donors, b) a consisting of one or more Me transporters, and c) a consisting of one or more bioflavonoids are well-suited for the treatment and prevention of transmethylation disorders, preferably cardiovascular diseases such as atherogenic and **thrombogenic** diseases. A compn. was prepd. contg. betaine 600, Ca L-5-methyltetrahydrofolate 0.5, and isoquercetin 500 mg.

L4 ANSWER 25 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:180852 CAPLUS
DOCUMENT NUMBER: 132:227421
TITLE: Methods for the lyophilization of living biological materials
INVENTOR(S): Wiggins, Philippa M.
PATENT ASSIGNEE(S): Biostore New Zealand, Ltd., N. Z.
SOURCE: U.S., 16 pp., Cont.-in-part of U.S. Ser. No. 60,770.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6040132	A	20000321	US 1998-85334	19980526
US 5879875	A	19990309	US 1996-662244	19960614
US 5827640	A	19981027	US 1996-722306	19960930
US 6114107	A	20000905	US 1997-842553	19970415
US 5962213	A	19991005	US 1997-989470	19971212
US 6060233	A	20000509	US 1998-60770	19980415
AU 742402	B2	20020103	AU 2001-10037	20010103

PRIORITY APPLN. INFO.:
US 1996-662244 A2 19960614
US 1996-722306 A2 19960930
US 1997-842553 A2 19970415
US 1997-989470 A2 19971212
US 1998-60770 A2 19980415
AU 1996-61412 A3 19960614
WO 1996-NZ57 Ad 19960614

AB The present invention provides methods for preserving living biol. materials by lyophilization that enable cells and tissues to be stored for extended periods of time with minimal loss of biol. activity. In one embodiment, the inventive methods comprise contacting a biol. material with a preservative soln. comprising either betaine or tri-Me amine oxide, together with sodium citrate and sodium chloride, reducing the temp. of the biol. material to less than 0.degree., and drying the biol. material to provide a freeze-dried material. The preservative solns. employed in the inventive methods are preferably isotonic with the material to be preserved and substantially free of iodide, dihydrogen phosphate, bicarbonate, nitrate and bisulfate. Blood platelets were resuspended at a concn. of 53x109/L in cold soln. contg. 45.8 mM NaCl, 184 mM tri-Me amine oxide, and 1.96 mM sodium citrate at a total osmolality of 0.29 OsM and

freeze-dried. Freeze-dried platelets were stored at room temp. and subsequently reconstituted by adding the same vol. of water that had been extd. during freeze drying. After the interval of 1.9 h, spontaneous aggregation was zero, **thrombin**-activated aggregation was over 80% and recovery 100%. After a time interval of 24 h, both **thrombin**-activated aggregation and platelet recovery were greater than 50%.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:537395 CAPLUS
DOCUMENT NUMBER: 132:34253
TITLE: The molecular basis of cystathionine .beta.-synthase deficiency in Dutch patients with homocystinuria: effect of CBS genotype on biochemical and clinical phenotype and on response to treatment
AUTHOR(S): Kluijtmans, Leo A. J.; Boers, Godfried H. J.; Kraus, Jan P.; Van den Heuvel, Lambert P. W. J.; Cruysberg, Johan R. M.; Trijbels, Frans J. M.; Blom, Henk J.
CORPORATE SOURCE: Department of Pediatrics, University Hospital Nijmegen, Nijmegen, 6500 HB, Neth.
SOURCE: American Journal of Human Genetics (1999), 65(1), 59-67
CODEN: AJHGAG; ISSN: 0002-9297
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Homocystinuria due to cystathionine .beta.-synthase (CBS) deficiency, inherited as an autosomal recessive trait, is the most prevalent inborn error of methionine metab. Its diverse clin. expression may include ectopia lentis, skeletal abnormalities, mental retardation, and premature arteriosclerosis and **thrombosis**. This variability is likely caused by considerable genetic heterogeneity. We investigated the mol. basis of CBS deficiency in 29 Dutch patients from 21 unrelated pedigrees and studied the possibility of a genotype-phenotype relationship with regard to biochem. and clin. expression and response to homocysteine-lowering treatment. Clin. symptoms and biochem. parameters were recorded at diagnosis and during long-term follow-up. Of 10 different mutations detected in the CBS gene, 833T.fwdarw.C (I278T) was predominant, present in 23 (55%) of 42 independent alleles. At diagnosis, homozygotes for this mutation (n = 12) tended to have higher homocysteine levels than those seen in patients with other genotypes (n = 17), but similar clin. manifestations. During follow-up, I278T homozygotes responded more efficiently to homocysteine-lowering treatment. After 378 patient-years of treatment, only 2 vascular events were recorded; without treatment, at least 30 would have been expected (P <.01). This intervention in Dutch patients significantly reduces the risk of cardiovascular disease and other sequelae of classical homocystinuria syndrome.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:87873 CAPLUS
DOCUMENT NUMBER: 128:216716
TITLE: No change in impaired endothelial function after long-term folic acid therapy of hyperhomocysteinemia in hemodialysis patients
AUTHOR(S): van Guldener, Coen; Janssen, Marrien J. F. M.;

09702165

Lambert, Jan; ter Wee, Piet M.; Jakobs, Cornelis; Donker, Ab J. M.; Stehouwer, Coen D. A.
CORPORATE SOURCE: Departments of Internal Medicine, Nephrology; and Clinical Chemistry and Paediatrics, University Hospital and Institute for Cardiovascular Research, Vrije Universiteit, Amsterdam, Neth.
SOURCE: Nephrology, Dialysis, Transplantation (1998), 13(1), 106-112
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hyperhomocysteinemia is frequent in chronic hemodialysis patients. Because of its potential role in athero- and **thrombogenesis**, the effects of long-term homocysteine-lowering treatment on endothelial function are of interest. We conducted a randomized, controlled trial in 35 hemodialysis patients. In phase 1, patients were treated with 5 mg folic acid or 5 mg folic acid and 4 g betaine per day for 12 wk, and in phase 2 with 1 or 5 mg folic acid daily for 40 wk. In phase 3, all patients received 15 mg folic acid daily for four weeks. Endothelial function was assessed before and after 52 wk of treatment by detn. of flow-mediated vasodilatation of the brachial artery, and by measuring plasma levels of endothelium-derived proteins. Non-fasting predialysis plasma total homocysteine was markedly elevated at baseline (46.9 .+-. 6.3 gmol/L) and decreased rapidly after initiation of therapy. Significant differences in plasma homocysteine between the groups were found neither during phase 1 nor phase 2. Plasma total homocysteine had normalized in only two out of 30 patients at the end of phase 2. Increasing the daily folic acid dose to 15 mg did not further reduce plasma total homocysteine. Endothelial function parameters did not improve. We concluded that betaine is not effective in conjunction with folic acid in the treatment of hyperhomocysteinemia in hemodialysis patients. Normalization of plasma total homocysteine is seldom achieved with 1, 5 or 15 mg folic acid daily, which may explain why long-term homocysteine-lowering treatment with 1 or 5 mg folic acid does not ameliorate endothelial function.

leads against

L4 ANSWER 28 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:7379 CAPLUS
DOCUMENT NUMBER: 128:110823
TITLE: Cytoprotection by the osmolytes betaine and taurine in ischemia-reoxygenation injury in the perfused rat liver
AUTHOR(S): Wettstein, Matthias; Haussinger, Dieter
CORPORATE SOURCE: Clinic for Gastroenterology, Hepatology, and Infectiology, Heinrich-Heine University, Dusseldorf, Germany
SOURCE: Hepatology (Philadelphia) (1997), 26(6), 1560-1566
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Medium osmolarity sensitively regulates Kupffer cell functions like phagocytosis and prostaglandin (PG) and cytokine prodn. Betaine and taurine, recently identified as osmolytes in liver cells, interfere with these effects. Because Kupffer cell activation is an important pathogenic mechanism in ischemia-reoxygenation injury, the influence of osmolarity and osmolytes was investigated in a rat liver perfusion model of warm ischemia. Livers were perfused with different medium osmolarities for 60 to 90 min in the absence of oxygen, followed by another 90 min of reoxygenation. Lactate dehydrogenase (LDH) leakage into the effluent

perfusate during the hypoxic and the reoxygenation period was eight- to 10-fold higher with a medium osmolarity of 385 mosmol/L than in normo-osmolarity, and further decreased with hypo-osmolar perfusion buffer. Betaine and taurine addn. to the perfusate in near physiol. concns. decreased hypoxia-reoxygenation-induced LDH leakage, aspartate transaminase (AST) leakage, and perfusion pressure increase in hyperosmolar and normo-osmolar perfusions. Stimulation of PGD2, PGE2, **thromboxane** B2 (TXB2), and tumor necrosis factor .alpha. (TNF-.alpha.) release, as well as induction of carbon uptake by the liver during reoxygenation, were suppressed by betaine and taurine, pointing to an interference of these osmolytes with Kupffer cell function. In contrast, endothelial cell function as assessed by hyaluronic acid (HA) uptake was not influenced. It is concluded that warm ischemia-reoxygenation injury in rat liver is aggravated by hyperosmolarity and attenuated by hypo-osmolarity. The osmolytes betaine and taurine have a protective effect, presumably by inhibition of Kupffer cell activation.

L4 ANSWER 29 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:696628 CAPLUS
DOCUMENT NUMBER: 127:326531
TITLE: Use of an osmolyte in the preparation of a medicament for treating complications resulting from ischemia
INVENTOR(S): Haussinger, Dieter
PATENT ASSIGNEE(S): Haussinger, Dieter, Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9738685	A1	19971023	WO 1997-EP1861	19970414
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2251071	AA	19971023	CA 1997-2251071	19970414
AU 9723860	A1	19971107	AU 1997-23860	19970414
EP 946167	A1	19991006	EP 1997-919356	19970414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2000508651	T2	20000711	JP 1997-536745	19970414
US 5880098	A	19990309	US 1997-878557	19970619
NO 9804759	A	19981012	NO 1998-4759	19981012

PRIORITY APPLN. INFO.: SE 1996-1396 A 19960412
WO 1997-EP1861 W 19970414

AB The present invention is directed to a therapy involving effective amts. of an osmolyte, e.g. taurine, betaine, or inositol capable of treating or preventing complications resulting from ischemia, hypoxia, or oxidative stress. Supplementation of certain osmolytes improves the endothelial cell functions and diminishes the inflammatory response of the immune competent cells. Kupffer cells from rats were cultured in RPMI 1640 medium supplemented with calf serum. Hypoxia resulted in LDH release demonstrating a deteriorating cell and organ integrity and function; treatment of the cells with 0.1 mM and 1 mM betaine soln. diminished the injury during and following hypoxia in a dose-dependent manner.

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L4 ANSWER 30 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:187374 CAPLUS
DOCUMENT NUMBER: 118:187374
TITLE: Method using two-component additive for stabilization of biomaterials during lyophilization
INVENTOR(S): Carpenter, John F.
PATENT ASSIGNEE(S): Cryolife, Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9300807	A1	19930121	WO 1992-US5643	19920702
W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO				
AU 9223096	A1	19930211	AU 1992-23096	19920702
PRIORITY APPLN. INFO.:			US 1991-725593	19910703
			WO 1992-US5643	19920702

AB A method for stabilizing biomaterials during lyophilization uses a two-component additive. The 1st component (PEG, dextran, ficoll, etc.) serves as a cryoprotectant, and the 2nd component (e.g. a sugar polyhydroxy alc., amino acid) protects the biomaterial (e.g. a protein) during drying. In freeze-drying lactate dehydrogenase M isoenzyme with PEG and a second component (trehalose, lactose, glucose, glycine, or mannitol), the results supported synergistic stabilization of the protein during freeze-drying.

L4 ANSWER 31 OF 31 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1964:33231 CAPLUS
DOCUMENT NUMBER: 60:33231
ORIGINAL REFERENCE NO.: 60:5956e-f
TITLE: Cardiovascular lesions in Swiss mice fed a high-fat low-protein diet with and without betaine supplementation
AUTHOR(S): Ball, Carroll R.; Williams, W. Lane; Collum, Julius M.
CORPORATE SOURCE: Univ. of Mississippi School of Med., Jackson
SOURCE: Anat. Record (1963), 145, 49-59
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Young adult Taconic Swiss mice weighing at least 22 g. were placed on a diet contg. 8% casein, 28% lard, 57.5% sugar, 4% salt mixt. In addn., 2% betaine-HCl was added as a lipotropic supplement in the diet and fed to half the mice. After 7 weeks on the diet with or without the betaine supplement, myocardial necrosis and **thrombi** within atrial lumina occurred. By 13 weeks, the **thrombi** reached lethal size for 75% of the animals. Loss of wt. paralleled the development and progress of the cardiac lesions. Liver showed parenchymal liposis, which was less severe in mice receiving betaine. The betaine did not prevent or alter the cardiovascular lesions.

L10 ANSWER 13 OF 13 CA COPYRIGHT 2003 ACS DUPLICATE 7
AN 55:9663 CA
OREF 55:1927e-f
TI Changes in **blood coagulation** in experimental subacute poisoning with p-dichlorobenzene. The influence of some lipotropic factors
AU Salamone, L.; Coppola, A.
CS Univ. Palermo, Italy
SO Folia Medica (Naples) (1960), 43, 259-66
CODEN: FOMDAK; ISSN: 0015-5608
DT Journal
LA Unavailable
CC 11H (Biological Chemistry: Pharmacology)
AB Guinea pigs were subacutely poisoned by intramuscular injections of a mixt. of equal parts of p-dichlorobenzene (I) and olive oil. This produced hepatic steatosis and prolongation of **blood coagulation** by redn. of the activity of the prothrombin complex, esp. of factor VII, prothrombin, and thromboplastin. Simultaneous administration of betaine, choline, and vitamin B12 showed a marked protective effect. The early appearance of the disturbance of **blood coagulation** suggests usefulness in diagnosis of I intoxication.
IT **Blood coagulation**
(p-dichlorobenzene effect on)
IT Liver
(p-dichlorobenzene effect on, **blood coagulation** and)
IT Thromboplastic substances, Thromboplastin
(p-dichlorobenzene effect on)
IT **107-43-7**, Betaine
(antagonism to CCl4 effect on visual purple regeneration, to p-dichlorobenzene effect on **blood coagulation**)
IT 62-49-7, Choline
(effect of p-dichlorobenzene and, on **blood coagulation**)
IT 106-46-7, Benzene, p-dichloro-
(effect on **blood coagulation**)
IT 68-19-9, Vitamin B12
(in **blood coagulation** response to p-dichlorobenzene)
IT 9001-25-6, Factor VII 9001-26-7, Prothrombin
(p-dichlorobenzene effect on)

=>

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 107-43-7 REGISTRY
CN Methanaminium, 1-carboxy-N,N,N-trimethyl-, inner salt (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ammonium compounds, substituted, (carboxymethyl)trimethyl-, hydroxide, inner salt (7CI)
CN Betaine (8CI)
CN Methanaminium, 1-carboxy-N,N,N-trimethyl-, hydroxide, inner salt
OTHER NAMES:
CN (Carboxymethyl)trimethylammonium hydroxide inner salt
CN (Trimethylammonio)acetate
CN .alpha.-Earleine
CN Abromine
CN Aminocoat
CN Aquadew AN 100
CN Betafin
CN Betafin BCR
CN Betafin BP
CN Cystadane
CN FinnStim
CN **Glycine betaine**
CN Glycine, trimethylbetaine
CN Glycocoll betaine
CN Glycylbetaine
CN Greenstim
CN Loramine AMB 13
CN Lycine
CN N,N,N-Trimethylglycine
CN Oxyneurine
CN Rubrine C
CN Trimethylglycine
CN Trimethylglycocoll
FS 3D CONCORD
DR 11042-12-9, 590-30-7, 24980-93-6, 45631-77-4
MF C5 H11 N O2
CI COM

09702165

L13 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:55671 CAPLUS
DOCUMENT NUMBER: 116:55671
TITLE: The influence of organic nitrogen sources on the induction of embryogenic callus in Agrostis alba L
AUTHOR(S): Shetty, Kalidas; Asano, Yoshito
CORPORATE SOURCE: Dep. Cell Biol., Natl. Inst. Agrobiol. Resour., Tsukuba, Japan
SOURCE: Journal of Plant Physiology (1991), 139(1), 82-5
CODEN: JPPHEY; ISSN: 0176-1617
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of certain org. nitrogen sources on the induction of embryogenic callus from mature seed of Agrostis alba was examd. Among the compds. tested were amino acids that are present in hydroxyproline-rich **glycoproteins**, polyamines, and osmolytes like proline, **glycine betaine**, and the **glycine betaine** precursor choline. Proline had a significant stimulatory effect on the induction of embryogenic callus. Among the other compds. tested, only glutamine was stimulatory, whereas most other compds. were inhibitory, particularly at higher concns.